

Hormone replacement treatment

Deserves wider use

Far fewer women in Britain than in North America are given hormone replacement treatment after the menopause. Yet a flood of material in the media is promoting the treatment. The innately conservative medical profession has met this with cautious uncertainty, but we need to look hard at the risks and benefits of hormone replacement treatment—particularly at symptomatic effects, cardiovascular sequelae, the impact on bones, and the risk of cancer.

The symptomatic response to the menopause is variable, and the severity of features such as flushing, insomnia, and depression bears no relation to the likelihood of developing myocardial ischaemia or osteoporosis. It is a myth that severely disabling symptoms fade within a couple of years in all women, and there is no question that hormone replacement treatment will relieve these symptoms.¹ The duration of treatment for these indications needs to be adjusted for each subject.

Atheroma accelerates after the menopause^{2,3}; Witteman and colleagues have recently shown a rapid increase in calcification of the abdominal aorta after the menopause⁴—such calcification predicts cardiovascular death.⁵ Large studies in the United States have shown that oestrogen treatment protects postmenopausal women from ischaemic heart disease^{6,7}; oestrogens also protect against stroke,⁸ and most women given oestrogens experience a fall in blood pressure.⁹ This abundant evidence leaves no room for doubt, yet many doctors remain suspicious that thrombotic disorders are promoted by oestrogens; they wrongly extrapolate from the experience of younger women who take oral contraceptives. It is in fact the cardiovascular benefits that largely account for the increased longevity in women receiving hormone replacement treatment.¹⁰

Bone loss accelerates in the decade after the menopause. Trabecular bone is most affected, causing wrist (Colles') and vertebral crush fractures. The later loss of cancellous bone has been attributed to aging itself and is particularly associated with fracture of the femoral neck.¹¹ Hormone replacement treatment protects against fractures of the wrist,¹² spine,¹³ and hip.¹²⁻¹⁶

Identifying women most at risk is best achieved by bone densitometry, and the benefits of treatment have been calculated.¹⁷ Facilities for measuring bone density fall far short of the need. Hormone replacement treatment is best used for preventing osteoporosis in women aged up to 60, but alternative treatments are more suitable for established osteo-

porosis in older women. Despite recent critical reappraisal of calcium supplementation to prevent osteoporosis^{18,19} much evidence shows that it restrains the rate of bone loss.^{20,21}

Most uncertainty and contention relate to hormone replacement treatment and the risk of cancer. Oestrogen is no longer given alone in women with an intact uterus because of the link with endometrial carcinoma.^{22,23} Fortunately this risk is virtually abolished by giving sufficient progestogen cyclically—current wisdom dictates that it is given for 10 to 12 days each month. Withdrawal bleeds are the necessary consequence, but these are usually brief, slight, and acceptable. Data conflict on the effect of hormone replacement treatment on breast cancer: some show that the risk is reduced²⁴ whereas other data suggest a slight increase.^{10,25} The concern is real because it may be a long time before an effect is seen clinically. In addition, with breast cancer already affecting one in 16 women a small enhancement of relative risk might yield a major increase in numbers of women with the disease. The length of experience with hormone replacement treatment in North America provides some reassurance.

Hormone replacement treatment is conventionally given as natural oestrogens. The oral route has been safely used widely, but the consequent first pass effect on liver metabolism, leading to variable oestrogen concentrations entering the systemic circulation and undesirable effects on hepatic factors involved in thrombosis, favours the use of alternative routes that deliver oestrogen into the systemic circulation directly. Oestrogen implants have long been used and still find ardent advocates, though concentrations of oestradiol may remain high for long periods.²⁶ The introduction of patches that permit predictable oestrogen absorption across the skin is welcome.²⁷

Hormone replacement treatment is not a panacea, and healthy bones and hearts may be achieved through exercise²⁸⁻³⁰ and diet. But there is now irrefutable evidence of the benefits of this treatment, and it should be offered to many more women in Britain.

PAUL BELCHETZ

Consultant Endocrinologist,
Leeds General Infirmary,
Leeds LS1 3EX

- 1 Campbell S, Whitehead MI. Oestrogens and the menopausal syndrome. In: Greenblatt RB, Studd JWW, eds. *Clinics in obstetrics and gynaecology: the menopause*. Vol 4. Philadelphia: Saunders, 1977:31-47.
- 2 Wuest JH, Dry TJ, Edwards JE. The degree of coronary atherosclerosis in bilaterally oophorectomized women. *Circulation* 1953;7:801-9.

- 3 Gordon T, Kannel WB, Hjortland MC, McNamara MP. Menopause and coronary heart disease: the Framingham study. *Ann Intern Med* 1978;**89**:157-61.
- 4 Witteman JCM, Grobee DE, Kok FJ, Hofman A, Valkenburg HA. Increased risk of atherosclerosis in women after the menopause. *Br Med J* 1989;**298**:642-4.
- 5 Witteman JCM, Kok FJ, van Saase JLCM, Valkenburg HA. Aortic calcification as a predictor of cardiovascular mortality. *Lancet* 1986;ii:1120-2.
- 6 Ross RK, Paganini-Hill A, Mack TM, Arthur M, Henderson BE. Menopausal oestrogen therapy and protection from death from ischaemic heart disease. *Lancet* 1981;ii:858-60.
- 7 Stampfer MJ, Willett WC, Colditz GA, Rosner B, Speizer FE, Hennekens CH. A prospective study of postmenopausal oestrogen therapy and coronary heart disease. *N Engl J Med* 1985;**313**:1044-9.
- 8 Paganini-Hill A, Ross RK, Henderson BE. Postmenopausal oestrogen treatment and stroke: a prospective study. *Br Med J* 1988;**297**:519-22.
- 9 Lind T, Cameron EC, Hunter WM, et al. A prospective controlled trial of six forms of hormone replacement therapy given to postmenopausal women. *Br J Obstet Gynaecol* 1979;**86** (suppl 3): 1-29.
- 10 Hunt K, Versey M, McPherson K, Coleman M. Long-term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy. *Br J Obstet Gynaecol* 1987;**94**: 620-35.
- 11 Riggs BL, Melton LJ III. Involutional osteoporosis. *N Engl J Med* 1986;**314**:1676-86.
- 12 Weiss NS, Ure CL, Ballard JH, Williams AR, Daling JR. Decreased risk of fractures of the hip and lower fore-arm with postmenopausal use of estrogen. *N Engl J Med* 1980;**303**:1195-8.
- 13 Munk-Jensen N, Nielsen SP, Obel EB, Eriksen PB. Reversal of postmenopausal vertebral bone loss by oestrogen and progestogen: a double blind placebo controlled study. *Br Med J* 1988;**296**:1150-2.
- 14 Paganini-Hill A, Ross RK, Gerkins VR, Henderson BE, Arthur M, Mack TM. Menopausal estrogen therapy and hip fractures. *Ann Intern Med* 1981;**95**:28-31.
- 15 Ettinger B, Genant HK, Cann CE. Long-term estrogen replacement therapy prevents bone loss and fractures. *Ann Intern Med* 1985;**102**:319-24.
- 16 Purdie DW. Broken bones—a gynaecological problem. *Br J Obstet Gynaecol* 1988;**95**:737-9.
- 17 Horsman A, Marshall DH. Age-related bone loss and fracture risk: a stochastic model. *Mathematical Modelling* 1986;**7**:991-1001.
- 18 Kanis JA, Passmore R. Calcium supplementation of the diet. I. *Br Med J* 1989;**298**:137-40.
- 19 Kanis JA, Passmore R. Calcium supplementation of the diet. II. *Br Med J* 1989;**298**:205-8.
- 20 Horsman A, Gallagher JC, Simpson M, Nordin BEC. Prospective trial of oestrogen and calcium in postmenopausal women. *Br Med J* 1977;ii:789-92.
- 21 Riis B, Thomsen K, Christiansen C. Does calcium supplementation prevent postmenopausal bone loss? *N Engl J Med* 1987;**316**:173-7.
- 22 Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. *N Engl J Med* 1975;**293**:1167-70.
- 23 Mack TM, Pike MC, Henderson BE, Pfeiffer RI, Gerkins VR, Arthur M. Estrogens and endometrial cancer in a retirement community. *N Engl J Med* 1976;**294**:1262-7.
- 24 Kaufman DW, Miller DR, Rosenberg L, et al. Noncontraceptive estrogen use and the risk of breast cancer. *JAMA* 1984;**252**:63-7.
- 25 Key TJA, Pike MC. The role of oestrogen and progestagens in the epidemiology and prevention of breast cancer. *Eur J Cancer Clin Oncol* 1988;**24**:29-43.
- 26 Savvas M, Studd JWW, Fogelman I, Dooley M, Montgomery J, Murby B. Skeletal effects of oral oestrogen compared with subcutaneous oestrogen and testosterone in postmenopausal women. *Br Med J* 1988;**297**:331-3.
- 27 Powers MS, Schenkel L, Darley PE, Good WR, Balestra JC, Place VA. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17 β -estradiol: comparison with conventional oral estrogens used for hormone replacement. *Am J Obstet Gynecol* 1985;**152**:1099-106.
- 28 Chow R, Harrison JE, Notarius C. Effect of two randomised exercise programmes on bone mass of healthy postmenopausal women. *Br Med J* 1987;**295**:1441-4.
- 29 Schapira D. Physical exercise in the prevention and treatment of osteoporosis—a review. *J R Soc Med* 1988;**81**:461-3.
- 30 Cooper C, Barker DJP, Wickham C. Physical activity, muscle strength, and calcium intake in fracture of the proximal femur in Britain. *Br Med J* 1988;**297**:1443-6.

Hypercalcaemia in malignancy

Fluids and bisphosphonate are best when life is threatened

Malignancy accounts for about half of the cases of hypercalcaemia seen in hospital,^{1,2} and around 5% of hospital patients with a malignancy have complicating hypercalcaemia. Carcinomas of the breast and lung account for nearly half of cases. About three quarters of those with hypercalcaemia have overt disseminated disease, and about four fifths die within a year. In only four of 219 consecutive patients whom we studied was hypercalcaemia recognised before malignant disease—and in three of them the malignancy was discovered immediately the patient was investigated.² Malignancy is only rarely the cause of hypercalcaemia in a patient who is well and is found by chance to be hypercalcaemic.

The symptoms of hypercalcaemia in malignancy are similar to those in other causes of hypercalcaemia,² being non-specific and including fatigue, anorexia, constipation, polydipsia, muscle weakness, nausea, and vomiting. Many of the symptoms may easily be attributed to the malignancy itself or to its treatment. Many patients with hypercalcaemia complicating a malignancy do not receive treatment for it, and when they do it is commonly not the most effective.

Despite the many previous theories of how malignancy causes hypercalcaemia only two survive: the production of a protein like parathyroid hormone by the tumour and the release of bone resorbing cytokines from secondary tumours in the bone. The hypercalcaemias of malignancy and hyperparathyroidism have many biochemical similarities,³ but parathyroid hormone itself is rarely if ever produced by malignant tumours. But much evidence supports the production of a factor like parathyroid hormone, and two groups have now isolated a novel protein that acts like parathyroid hormone but is immunologically distinct.^{4,5}

Unfortunately, many different names have been attached to the protein; it is referred to here as parathyroid hormone related protein. It consists of a 141 amino acid polypeptide whose initial 13 amino acids show a 61% homology with parathyroid hormone; other areas of the molecule show little if any homology. All the known biological activity of the protein resides in the first 34 amino acids, and synthetic analogues of the 1-34 fragment of the protein as well as the entire molecule have all the biological actions of para-

thyroid hormone: they are usually at least as potent as parathyroid hormone—and in some assays are more so.^{6,8} Parathyroid hormone related protein is particularly potent when given parenterally. The protein has been identified in a wide range of solid tumours complicated by hypercalcaemia, and antibodies to it alleviate hypercalcaemia in animal models of hypercalcaemia of malignancy.⁹ It is probably responsible for the hypercalcaemia of many or most of the patients seen in clinical practice.

Several bone resorbing cytokines have now been identified, including interleukin-1,¹⁰ transforming growth factors,^{11,12} epidermal growth factor,¹³ tumour necrosis factor,¹⁴ and platelet derived growth factor.¹⁵ In addition, prostaglandin E₂ resorbs bone in vitro.¹⁶ Except under exceptional circumstances none of these factors causes hypercalcaemia when given parenterally. But many are produced by tumours and if produced locally in bone from metastases they might cause appreciable osteolysis and release calcium into the circulation. Yet there is no correlation between hypercalcaemia and the number of bone metastases. If, therefore, locally active cytokines are produced by many secondary tumours in bone the body may be able to eliminate the calcium released and prevent hypercalcaemia.

The two hypotheses may be combined to explain most circumstances in which hypercalcaemia occurs. Many tumours (particularly those of epithelial origin) produce parathyroid hormone related protein. To begin with not enough is produced to cause hypercalcaemia, but occasionally sufficient is secreted, and hypercalcaemia and rarely “hyperparathyroid bone disease” result.¹⁷ Increased tumour mass leads to greater production of the protein and a greater chance of hypercalcaemia. Secondary tumours in bone release locally active cytokines that cause osteolysis. Under normal circumstances the excess calcium is excreted, but if the tumour also produces parathyroid hormone related protein the two mechanisms will be additive and make it much more difficult for normocalcaemia to be maintained.

All patients with a malignancy who feel unwell should have their serum concentrations of calcium and albumin or total protein measured. Measuring albumin and total protein